DETAILED ACTION

Claims 1-56 are pending.
Claims 1, 3-12, and 14-56 are withdrawn from examination as detailed below.
Claims 2 and 13 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of the invention of Group 2 (i.e. nucleic acid based methods for the in vitro detection of sepsis and/or sepsis-like conditions) in the reply filed on 11/20/2008 is acknowledged. The traversal is on the ground(s) that 'measurement of levels of genes' (Remarks p.11) is the common technical feature among the different groups. This is not found persuasive because the measurement of levels of gene expression in the analysis of sepsis and inflammation was known in the prior art at the time the invention was made (i.e. as taught in Chinnaiyan et al (1999) cited in the Lack of Unity Requirement for Restriction of 08/20/2008). Thus this common technical feature is not a special technical feature in view of the prior art, And does not provide unity of invention. And while Applicants submit that the inventions of claims 2, 3, 13, and 14 would be obvious over each other, the express admission of obviousness is noted; but in the instant case the application is a national stage application of a PCT where Lack of Unity rules apply to separation of different inventions, and the Examiner maintains that the different invention of the claims are properly separable under Lack of Unity rules.

Applicant's further election with traverse of the invention of particular combination of sequences of those sequences recited on pages 13-14 of the Remarks with the

'Patent Seq ID' of Roman numeral 'I' (see the interview summary where the recited sequences with Roman numeral 'II' (i.e. the last 15 sequences on page 14 of the Remarks with SEQ ID NOs: in the ranges of 6250-6366) are not included in the Election) in the reply filed on 11/20/2008 is acknowledged. The traversal is on the ground(s) that 'sepsis conditions are determined not by qualitative measurement of any particular genes, but quantitative measurement. Thus, to require restriction of the invention to any particular combination of gene s indicates that the invention is not understood' (Remarks p.14). This is not found persuasive because, regardless of the type of measurement (i.e. qualitative or quantitative) the different nucleic acid sequences are structurally distinct elements, as set forth on page 3 of the Requirement of 08/20/2008.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 3-12 and 14-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/20/2008.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on the following applications filed in Germany:

103 15 031 5 filed on 04/02/2003

103365.7 filed on 08/08/2003

103 40 395.7 filed on 09/02/2003

It is noted, however, that applicant has not filed a certified copy of the foreign applications as required by 35 U.S.C. 119(b).

Objection to the claims and Specification - Sequence Compliance

4. This application contains references to sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 at least for the reason(s) set forth below. In particular, 37 CFR 1.821 (d) requires:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In the instant application, the specification does not use the proper format for the sequence identifier, where formats such as: 'SEQ. ID No.' (see ¶39-41, ¶66-68; ¶123; ¶148; ¶152; ¶167); 'SEQUENCE-ID' (Tables 2, 3, 5, 6, 8, 9, 12, 13; 'Sequenz-ID' (Figures 1 and 2); and 'SEQUENCE ID No. I.' (claim 13).

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), the specification and claims should be amended to included the proper format for the sequence identifier as set forth in 37 CFR 1.821.

Specification

5. The disclosure is objected to because of the following informalities:

In the specification, ¶130 references Tables 2 and 3, where likely reference to Tables 8 and 9 is intended. Applicants should review ¶130 to ensure that the appropriate tables are referenced.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example pages 22, 26, 31, and 42. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code from throughout the specification. See MPEP § 608.01.

Appropriate correction is required.

Claim Objections

6. Claim 2 is objected to over recitation of the phrase 'isolating of sample RNA from a sample of a mammal', where the phrase 'isolating sample RNA from a sample from a mammal' is correct.

7. Claim 13 is objected to for the specific recitation of non-elected subject matter. Applicants have elected for the specific combination of genes with the sequences as set forth in the first 57 sequences identified in the Table on pages 13-14 of the Remarks of 11/20/2008. Claim 13 encompasses any combination of 'SEQUENCE ID No, I.1 to SEQUNCE ID No. I.6242', thus encompassing numerous combinations and subcombinations of sequences different than the specific elected combination. It is noted that no claim is allowed in this Office Action. Upon allowance of a claim directed to the elected invention, the Examiner may consider rejoinder of the subject matter of the non-elected combinations, and rejoinder of any combinations that include all of the limitations of the allowed elected subcombination. Prior to allowance, any non-elected

subject matter that is not re-joined with the elected subject matter will be required to be removed from the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 13 are unclear over the purpose of the claimed methods ‘for in vitro detection of sepsis and/or sepsis-like conditions’ as recited in the preamble of claim 2. Claim 2 recites the methods steps of the claim as isolating and labeling RNA from a sample, contacting RNA with DNA, and detecting and comparing label signals. The final active process step is comparing label signals. There is no active step in which sepsis or a sepsis-like condition is in fact detected. Thus there is not a nexus between the purpose of the claimed method as stated in the preamble of claim 2 and the methods steps, and it is unclear how the performance of the methods steps results in the required 'detection of sepsis and/or sepsis-like conditions’.

Claims 2 and 13 are unclear over recitation of the phrase ‘contacting the sample RNA with the DNA under hybridization conditions’ because, with regard to the phrase ‘the DNA' the only prior recitation of 'DNA' is in the alternative 'sample RNA and/or at

least one DNA'. Thus there is no definitive requirement for DNA and there is a lack of sufficient antecedent basis for 'the DNA' in the phrase 'contacting the sample RNA with the DNA under hybridization conditions'. See MPEP 2173.05(e).

Claim 13 is unclear over recitation of the phrase 'the gene or gene segment' because there is a lack of sufficient antecedent basis for any 'gene segment'. See MPEP 2173.05(e).

Claim Rejections - 35 USC § 112 1st ¶ - Written Description

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 2 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants may wish to consult the Written Description Training Materials revised March 25, 2008, available online at www.uspto.gov/web/menu/written.pdf.

The rejection of claims for lack of adequate written description is relevant to the requirement of the claims, drawn to methods for in vitro detection of sepsis and/or sepsis-like condition, for RNA or DNA 'being a gene or gene fragment specific for sepsis' (as recited in claim 2), and 'gene fragments thereof with' as few as 5 nucleotides

(as recited and encompassed by claim 13). In the instant case the specification does not provide the skilled artisan with an adequate written description of particular nucleic acids suitable for performing the claimed method as generically encompassed by the claim 2 and minimally comprising 5 nucleotides as encompassed by claim 13.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant case, genes the expression of which is diagnostically indicative of sepsis or sepsis-like conditions are not known in the prior art (as generically recited in the claims, encompassing any genes or gene fragments from any subject mammal organism). Further, while the specification asserts that there is a group of gene from humans that are differentially expressed in humans with sepsis as compared to a non-septic individual (i.e. Tables 8 and 9), there is no disclosed relationship between the structure of the genes (i.e. their nucleotide sequences) and their functionality (i.e. diagnostic of sepsis). This is also relevant to the breadth of claim 13, which, consonant with the election, which encompasses any genes comprising as few as 5 nucleotides of the mRNA sequences as elected.

In conclusion, having considered the breadth of the claims, and the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of methods requiring the step of, for example:

> Comparing the abundance of particular mRNA species from a sample to the abundance of the same mRNA species from a control sample, wherein the mRNA species comprise SEQ ID NOs: 220, 3O3, 529, 754, 844, 1705, 2370, 2449, 2468, 2481, 2709, 2831, 2928, 2948, 3068, 3079, 3209, 3268, 3305, 3317, 3331, 3399, 3424, 3433, 3482, 3508, 3523, 3624, 3676, 3765, 3796, 3873, 3879, 3881, 3917, 4060, 4096, 4122, 4141, 4268, 4328, 4450, 4528, 4609, 4654, 4695, 4705, 4937, 5265, 5338, 5418, 5542, 5567, 5647, 5779, 6018 and 6200

does not provide an adequate written description of the broadly claimed subject matter.

Claim Rejections - 35 USC § 112 1st ¶ - Enablement

12. Claims 2 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims are drawn to methods of detection of sepsis and/or sepsis like conditions.

The claims encompass the analysis of any subject mammal.

The claims generically encompass analysis of any gene or fragment specific for sepsis.

The claims encompass any comparison of any labeled RNA, as well as any fragments of the elected combination of SEQ ID NOs..

The claims encompass detection of any condition that can be considered a ‘sepsis-like condition’.

The claims thus require knowledge of a correlative association between any expression levels of a wide variety of RNA combinations and a variety of different phenotypes in different subjects.

Direction provided by the specification and working example

Relevant to the Election, the instant specification provides a comparative analysis (Example 3 – p.26) of gene expression in two human individuals, one classified as a sepsis patient and the other classified as a non-septic control subject (Table 7). The specification provides asserts that 54 particular genes were overexpressed in the sepsis-patient sample (Table 8), and 56 particular gene were under-expressed in the sepsis-patient sample (Table 9).

Relevant to the claims and the elected invention, the specification provides the aforementioned analysis of sepsis gene expression, but does not provide for gene expression in the generic 'sepsis-like conditions'.

The specification does not provide any analysis of any other non-human subject organisms.

The specification provides only the results of a comparison between two individual subjects (a single case and a single control), with no validation of the asserted particular mRNAs specific for sepsis, nor any analyses of populations of cases or controls. There is no statistical analysis of the reliability of classification using expression of particular mRNA species.

Additionally it is noted that the particular mRNAs asserted in the specification (Tables 8 and 9) to be indicative of sepsis are not included in the particular mRNAs of the Election.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to determining the abundance of any particular nucleic acid biomarker or combination of biomarkers is high, the unpredictability associated with correlating any comparison of abundances with a particular phenotype such as sepsis, is even higher. Such unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

Because the claims encompass the analysis of biomarkers from any subject mammal, whereas the instant specification provides only an anlysis of human subjects, it is relevant to point out the unpredictability in extrapolating gene expression results among different organisms. Such unpredictability is exemplified by Hoshikawa et al (2003), which teaches unpredictability with regard to applying gene expression results among different organisms. The reference teaches the analysis of gene expression in lung tissue in response to hypoxic conditions which lead to pulmonary hypertension (Fig. 1). The reference teaches that the gene expression profile in mouse is different from that observed in rat (Tables 1-4; p.209 - Abstract). Thus it is unpredictable as to whether or not any genes that are sepsis-related in, for example, human are in fact applicable to predicting sepsis in any other non-human organism.

Because the claims encompass comparing any abundances of any particular RNAs to any control RNAs, where the specification provides only the example of analysis of two individuals (one case and one control), it is relevant to point out the unpredictability in using gene expression to establish a phenotype. For example, Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Additionally, the prior art of Shalon et al (2001) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158). Further, it is known in the art that the p-value of any marker used to diagnose sepsis will change based on the size of the population used for comparison (PG Pub US 2004/0106142, p.14, ¶[0127]).

Given the lack of any statistical significance in the methods, it is relevant to point out that the prior art of Thisted (1998) provides guidance as to what is required to

indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion).

Because claims encompass the analysis of gene expression in any tissue types, whereas the specification provides only expression in whole blood samples, it is relevant to point out the unpredictability in comparing gene expression among different tissues. Cobb et al (2002) teaches the unpredictability in analysis of gene expression different tissues of a septic mammal, specifically in spleen and liver samples from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., lns.2-8).

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to establish that any level of nucleic acid abundance of any RNAs, as compared to value in any control, is indicative of sepsis. Such experimentation would require case:control analysis of any subject mammal of interest, and require the analysis of different tissue types and analysis of any RNA species of interest. Even for the particularly elected SEQ ID NOs it is noted that the instant specification does not provide that these

mRNAs are robustly and reliably diagnostic of the presence of sepsis or any other condition that may be considered 'sepsis-like'.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Claim Rejections - 35 USC § 102

It is noted that claim rejected under 35 USC 102 as anticipated by the prior art have been previously rejected under 35 USC 112 1st ¶ for lack of enablement. In the instant case while the cited prior art meets all of the recited limitations of the rejected claim, the prior art is not enabling for the claim because the instant specification does not particularly contemplate nor specifically disclose the same analyses as the cited prior art.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Chinnaiyan et al (2001) (as cited on the IDS of 3/15/2006).

Chinnaiyan et al teach the analysis of gene expression in a sepsis model. Relevant to the rejected claims, the reference teaches isolating a sample of RNA from the subject mammal and labeling the sample RNA, contacting the sample RNA with DNA under hybridization conditions and analysis of RNA from a non-pathological control, and quantitative detection of labels (p.1200 - Rat model of sepsis; Microarray analysis). The microarray analysis of the reference comprises comparing the subject and control signals to determine expression levels as compared to each other (e.g. Fig. 2).

Conclusion

15. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/
Art Unit 1634